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(54) Title: NOVEL COMPOUNDS

(57) Abstract: The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders.



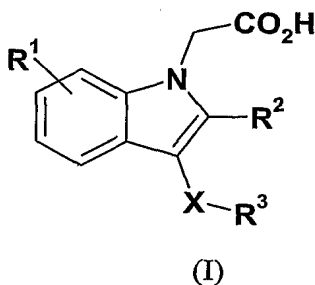
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NOVEL COMPOUNDS

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D₂, a ligand for orphan receptor CRTh₂. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. WO2003101961, WO2004007452, WO2004106032, WO2005018529 and WO2005019171 disclose a series of mono-aryl or mono-heteroaryl substituted indole acetic acids which are active at the CRTh₂ receptor. It has now surprisingly been found that certain bi-aryl or aryl-heteroaryl substituted indoles are active at the CRTh₂ receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

X is O or S(O)_n where n is 0, 1 or 2;

R¹ is hydrogen, halogen, CN, nitro, S(O)_nR⁴, OH, OR⁴, OS(O)_nR⁴, S(O)_nR⁴, SO₂NR⁵R⁶, CONR⁵R⁶, NR⁵R⁶, NR⁴SO₂R⁵, NR⁴CO₂R⁶, NR⁴COR⁶, NR⁴SO₂NR⁵R⁶, NHSO₂R⁵,

NHCO_2R^6 , NHCOR^6 , NHCONR^4 , $\text{NHSO}_2\text{NR}^5\text{R}^6$, aryl, heteroaryl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl or C_{1-6} alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^8 , NR^5R^6 and $\text{S(O)}_n\text{R}^7$ where n is 0, 1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 , CONR^5R^6 , CH_2OH , CH_2OR^4 , C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, OR^8 , NR^5R^6 or $\text{S(O)}_n\text{R}^7$ where n is 0, 1 or 2;

R^3 is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, $\text{S(O)}_n\text{R}^4$, OH, OR^4 , $\text{OS(O)}_n\text{R}^4$, $\text{S(O)}_n\text{R}^4$, $\text{SO}_2\text{NR}^5\text{R}^6$, CONR^5R^6 , NR^5R^6 , $\text{NR}^4\text{SO}_2\text{R}^5$, $\text{NR}^4\text{CO}_2\text{R}^6$, NR^4COR^6 , $\text{NR}^4\text{SO}_2\text{NR}^5\text{R}^6$, NHSO_2R^5 , NHCO_2R^6 , NHCOR^6 , NHCONR^4 , $\text{NHSO}_2\text{NR}^5\text{R}^6$, aryl, heteroaryl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl or C_{1-6} alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^8 , NR^5R^6 or $\text{S(O)}_n\text{R}^7$ where n = 0, 1 or 2;

R^4 represents aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl all of which may be optionally substituted by one or more substituents independently selected from hydrogen, halogen atoms, aryl, heteroaryl, OR^{10} , $\text{NR}^{11}\text{R}^{12}$, $\text{S(O)}_n\text{R}^{13}$ (where n = 0, 1 or 2), $\text{CONR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{COR}^{15}$, $\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{SO}_2\text{R}^{15}$, CN or nitro;

R^5 and R^6 independently represent a hydrogen atom, aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} , $\text{NR}^{11}\text{R}^{12}$, $\text{S(O)}_n\text{R}^{13}$ (where n = 0, 1 or 2), $\text{CONR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{COR}^{15}$, $\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{SO}_2\text{R}^{15}$, CN or nitro;
or

R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n where n = 0, 1 or 2, or NR^{16} , and itself optionally substituted by C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^7 and R^{13} independently represent aryl, heteroaryl, C_{3-8} cycloalkyl and C_{1-6} alkyl, all of which may be optionally substituted by one or more halogen atoms, aryl, heteroaryl, OR^{10} , $NR^{11}R^{12}$, $S(O)_nR^{13}$ (where $n = 0, 1$ or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$, $SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN or nitro;

R^8 represents a hydrogen atom, $C(O)R^9$, aryl, heteroaryl or C_1-C_6 alkyl (optionally substituted by one or more halogen atoms, aryl or heteroaryl);

each of R^9 , R^{10} , R^{11} , R^{12} , R^{14} and R^{15} independently represents a hydrogen atom, C_3-8 cycloalkyl, C_1-C_6 alkyl, an aryl or a heteroaryl group (all of which may be optionally substituted by one or more halogen atoms); and

R^{16} is hydrogen, C_{1-4} alkyl, $-COC_{1-4}$ alkyl, $COYC_{1-4}$ alkyl where Y is O, $S(O)_nR^{13}$ (where $n = 0, 1$ or 2) or NR^7 .

Provided that:

- One or more of the substituents on R^3 must be aryl, heteroaryl or C_{1-6} alkyl (the latter group being substituted by aryl or heteroaryl);
- When R^3 is biphenyl, X must be O or S;
- When R^3 is aryl substituted by C_{1-6} alkyl, X must be O or S;
- R^3 cannot be 4-phenyl-1,3-thiazol-2-yl.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear, branched or cyclic.

Aryl is phenyl or naphthyl, preferably phenyl.

Heteroaryl is defined as a 5-7 membered aromatic ring or can be 6,6- or 6,5-fused bicyclic each ring containing one or more heteroatoms selected from N, S and O. Examples include but are not limited to pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline,

isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, 1,2benzisothiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone.

When R^5 and R^6 together with the nitrogen to which they are attached form a 3-8 membered saturated heterocyclic ring examples include but are not limited to morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine. Substituents can be present on carbon or appropriate nitrogen atoms of such rings.

The term alkyl, whether alone or as part of another group, includes straight chain, branched or cyclic alkyl groups.

Except where otherwise stated aryl or heteroaryl groups can be optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, $S(O)_nR^4$, OH, OR^4 , $OS(O)_nR^4$, $S(O)_nR^4$, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6 , $NR^4SO_2R^5$, $NR^4CO_2R^6$, NR^4COR^6 , $NR^4SO_2NR^5R^6$, $NHSO_2R^5$, $NHCO_2R^6$, $NHCOR^6$, $NHCONR^4$, $NHSO_2NR^5R^6$, aryl, heteroaryl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl or C_{1-6} alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^8 , NR^5R^6 or $S(O)_nR^7$ where $n = 0, 1$ or 2 ;

Preferably X is $S(O)_n$ where n is 0, 1 or 2; more preferably X is S.

Preferably R^1 is halogen or $NHCOR^6$. More preferably R^1 is fluoro or $NHCOMe$.

Preferably R^2 is C_{1-7} alkyl; more preferably R^2 is C_{1-4} alkyl, most preferably methyl.

Preferably R^3 is aryl optionally substituted by the groups defined above. More preferably R^3 is phenyl optionally substituted by the groups defined above. Most preferably R^3 is phenyl substituted by phenyl, or a 5-membered heteroaryl group, preferably oxazolyl.

Preferred compounds of the invention include:

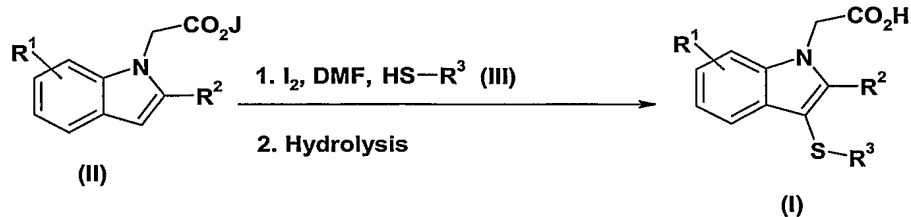
[3-(Biphenyl-4-ylsulfanyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid;
[5-Fluoro-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]acetic acid;
[4-Acetylamino-3-(biphenyl-4-ylsulfanyl)-2-methyl-indol-1-yl]-acetic acid;
[4-Acetylamino-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]-acetic acid
and pharmaceutically acceptable salts thereof.

Certain compounds of formula (I) are capable of existing in stereo isomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as ammonium, sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chlorprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

Compounds of formula (I) in which X is S can be prepared as outlined in Scheme 1:



Scheme 1

In which R^1 , R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof. J is hydrogen or alkyl for example methyl, ethyl or tert-butyl. Iodine is added to compounds of formula (II) and formula (III) in a suitable solvent such as DMF at a suitable temperature such as room temperature. Where J is alkyl, hydrolysis of the resulting ester is carried out using standard conditions, for example where J is methyl or ethyl hydrolysis can be carried out using sodium hydroxide. Alternatively where J is hydrogen the sulfide formation can be carried out directly on an acid of formula (II) to give compounds of formula (I) without subsequent hydrolysis.

Compounds of formula (II) are commercially available or can be prepared by methods well known in the art or alternatively can be prepared using methods described in WO2003101961, WO2004007451, WO2004007452, WO2004106032, WO2005018529 and WO2005019171.

Compounds of formula (III) are commercially available or can be prepared by methods well known in the art.

The compounds of formula (I) or pharmaceutically acceptable salts thereof have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever

and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);
4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvovaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;
12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;
13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;
14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting

the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. gastrointestinal tract: Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

16. Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CCR2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β_2 -receptor agonists and oral leukotriene receptor antagonists).

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic

obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1,

CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine,

terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a COMT inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming

growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;

- (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);
- (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;
- (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin);
- (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;
- (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or
- (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein

before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) the title and sub-titled compounds of the examples and methods were named using the ACD labs/name program (version 8.0) from Advanced Chemical Development Inc, Canada;
- (ii) unless stated otherwise, reverse phase preparative HPLC (RPHPLC) was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;
- (iii) flash column chromatography refers to normal phase silica chromatography;
- (iv) solvents were dried with MgSO_4 or Na_2SO_4 ;
- (v) Evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (vi) Unless otherwise stated, operations were carried out at ambient temperature, that is in the range 10-40°C and under an atmosphere of an inert gas such as argon or nitrogen;
- (vii) yields are given for illustration only and are not necessarily the maximum attainable;
- (viii) the structures of the end-products of formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet. ^1H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
- (ix) intermediates were characterised by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), infra-red (IR) or NMR analysis;

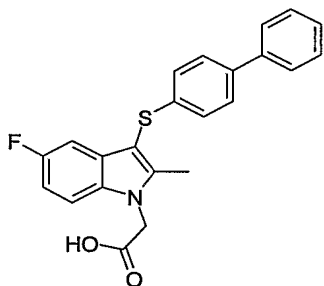
(x) mass spectra (MS): generally only ions which indicate the parent mass are reported when given; MM = MultiMode;

(xi) the following abbreviations are used:

EtOAc	Ethyl acetate
DMF	<i>N,N</i> -Dimethyl formamide
NMP	<i>N</i> -Methylpyrrolidinone
MgSO ₄	Magnesium sulphate
THF	Tetrahydrofuran
RT	Room temperature

Example 1

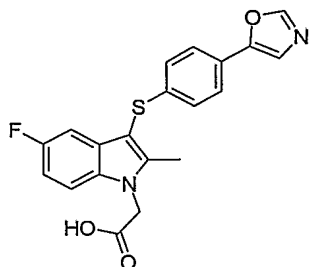
[3-(Biphenyl-4-ylsulfanyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid



To a solution of (5-fluoro-2-methyl-indol-1-yl)-acetic acid (0.5 g) and biphenyl-4-thiol (0.19 g) in DMF (5ml) was added iodine (0.25 g). After stirring at RT overnight the mixture was poured into water, the pH adjusted to 3 using 1M HCl and the organics extracted with EtOAc. The EtOAc extractions were combined, washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give crude material. Purification using RPHPLC gave the title compound as a pink solid (0.11g).

MS: MM(-ve): 390.2 (M-H).

¹H NMR (400 MHz, DMSO) δ 7.60 - 7.56 (m, 3H), 7.53 - 7.50 (m, 2H), 7.44 - 7.39 (m, 2H), 7.34 - 7.29 (m, 1H), 7.11 - 7.00 (m, 4H), 5.15 (s, 2H), 2.45 (s, 3H).

Example 2**[5-Fluoro-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]acetic acid****(i) 4-Oxazol-5-yl-benzenethiol**

To a solution of 4-oxazol-5-yl-benzenesulfonyl chloride (1 g) in THF (20 ml) was added triphenylphosphine (4.3 g). After stirring at RT for 10 minutes water (2 ml) was added and the reaction was stirred for a further 20 minutes. The reaction was evaporated under reduced pressure and the residue dissolved in EtOAc. The EtOAc solution was extracted with 1M NaOH (x3), the basic extractions were combined, the pH adjusted to 3 using 1M HCl and then re-extracted with EtOAc (x3). The EtOAc fractions were combined and washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound as a green solid (0.65 g).

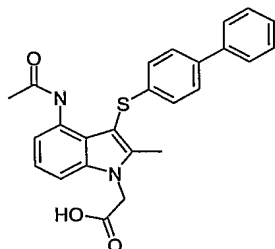
¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.54 - 7.50 (m, 2H), 7.34 - 7.31 (m, 3H), 3.53 (s, 1H).

(ii) [5-Fluoro-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]acetic acid

The title compound was prepared by the method of example 1 using the product from step (i).

MS: MM(-ve): 381 (M-H).

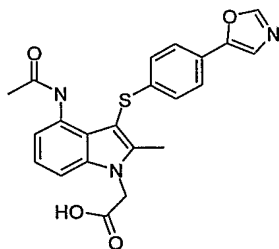
¹H NMR (400 MHz, DMSO) δ 8.38 (s, 1H), 7.61 - 7.55 (m, 4H), 7.09 - 7.00 (m, 4H), 5.15 (s, 2H), 2.43 (s, 3H).

Example 3**[4-Acetylamino-3-(biphenyl-4-ylsulfanyl)-2-methyl-indol-1-yl]-acetic acid**

To a solution of (4-acetylamino-2-methyl-indol-1-yl)-acetic acid ethyl ester (0.27 g) and biphenyl-4-thiol (0.19 g) in DMF (5 ml) was added iodine (0.25 g). After stirring at RT overnight 1M NaOH (3ml) was added and the reaction stirred at RT for a further 12 hours. The reaction was poured into water, the pH adjusted to 3 using 1M HCl and the organics extracted with EtOAc. The EtOAc extractions were combined, washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give crude material. Purification using RPHPLC gave the title compound as a pink solid (0.16 g).

MS: MM(-ve): 429.2 (M-H).

¹H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 7.61 - 7.52 (m, 5H), 7.42 (t, J = 7.6 Hz, 2H), 7.35 - 7.30 (m, 2H), 7.14 - 7.06 (m, 3H), 5.13 (s, 2H), 2.43 (s, 3H), 1.88 (s, 3H).

Example 4**[4-Acetylamino-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]-acetic acid**

The title compound was prepared by the method of example 3 using (4-acetylamino -2-methyl-indol-1-yl)-acetic acid ethyl ester and the product of example 2 step (i).

MS: MM(+ve): 422 (M+H).

¹H NMR (400 MHz, DMSO) δ 9.53 (s, 1H), 8.38 (s, 1H), 7.59 - 7.54 (m, 3H), 7.49 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.11 - 7.03 (m, 3H), 4.74 (s, 2H), 2.39 (s, 3H), 1.85 (s, 3H).

Pharmacological Data

Ligand Binding Assay

[³H]PGD₂ was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEK cells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100µg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4 ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25µg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

Each assay contained 20µl of 6.25nM [³H]PGD₂, 20µl membrane saturated SPA beads both in assay buffer and 10µl of compound solution or 13,14-dihydro-15-keto

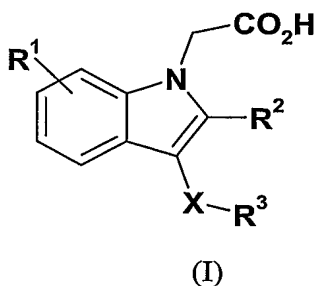
prostaglandin D₂ (DK-PGD₂, for determination of non-specific binding, Cayman chemical company).

Compounds and DK-PGD₂ were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at RT for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC₅₀ value of less than (<) 10μM. Specifically example 1 has a pIC₅₀ of 7.7.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

X is O or S(O)_n where n is 0, 1 or 2;

R¹ is hydrogen, halogen, CN, nitro, S(O)_nR⁴, OH, OR⁴, OS(O)_nR⁴, S(O)_nR⁴, SO₂NR⁵R⁶, CONR⁵R⁶, NR⁵R⁶, NR⁴SO₂R⁵, NR⁴CO₂R⁶, NR⁴COR⁶, NR⁴SO₂NR⁵R⁶, NHSO₂R⁵, NHCO₂R⁶, NHCOR⁶, NHCONR⁴, NHSO₂NR⁵R⁶, aryl, heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈cycloalkyl or C₁₋₆ alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR⁸, NR⁵R⁶ and S(O)_nR⁷ where n is 0, 1 or 2;

R² is hydrogen, halogen, CN, SO₂R⁴, CONR⁵R⁶, CH₂OH, CH₂OR⁴, C₃₋₈cycloalkyl or C₁₋₇alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, OR⁸, NR⁵R⁶ or S(O)_nR⁷ where n is 0, 1 or 2;

R³ is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, S(O)_nR⁴, OH, OR⁴, OS(O)_nR⁴, S(O)_nR⁴, SO₂NR⁵R⁶, CONR⁵R⁶, NR⁵R⁶, NR⁴SO₂R⁵, NR⁴CO₂R⁶, NR⁴COR⁶, NR⁴SO₂NR⁵R⁶, NHSO₂R⁵, NHCO₂R⁶, NHCOR⁶, NHCONR⁴, NHSO₂NR⁵R⁶, aryl, heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈cycloalkyl or C₁₋₆ alkyl, the latter four

groups being optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^8 , NR^5R^6 or $\text{S(O)}_n\text{R}^7$ where $n = 0, 1$ or 2 ;

R^4 represents aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl all of which may be optionally substituted by one or more substituents independently selected from hydrogen, halogen atoms, aryl, heteroaryl, OR^{10} , $\text{NR}^{11}\text{R}^{12}$, $\text{S(O)}_n\text{R}^{13}$ (where $n = 0, 1$ or 2), $\text{CONR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{COR}^{15}$, $\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{SO}_2\text{R}^{15}$, CN or nitro;

R^5 and R^6 independently represent a hydrogen atom, aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} , $\text{NR}^{11}\text{R}^{12}$, $\text{S(O)}_n\text{R}^{13}$ (where $n = 0, 1$ or 2), $\text{CONR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{COR}^{15}$, $\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{SO}_2\text{R}^{15}$, CN or nitro;
or

R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n where $n = 0, 1$ or 2 , or NR^{16} , and itself optionally substituted by C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^7 and R^{13} independently represent aryl, heteroaryl, C_{3-8} cycloalkyl and C_{1-6} alkyl, all of which may be optionally substituted by one or more halogen atoms, aryl, heteroaryl, OR^{10} , $\text{NR}^{11}\text{R}^{12}$, $\text{S(O)}_n\text{R}^{13}$ (where $n = 0, 1$ or 2), $\text{CONR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{COR}^{15}$, $\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{SO}_2\text{R}^{15}$, CN or nitro;

R^8 represents a hydrogen atom, C(O)R^9 , aryl, heteroaryl or $\text{C}_1\text{-C}_6$ alkyl (optionally substituted by one or more halogen atoms, aryl or heteroaryl);

each of R^9 , R^{10} , R^{11} , R^{12} , R^{14} and R^{15} independently represents a hydrogen atom, C_{3-8} cycloalkyl, $\text{C}_1\text{-C}_6$ alkyl, an aryl or a heteroaryl group (all of which may be optionally substituted by one or more halogen atoms); and

R^{16} is hydrogen, C_{1-4} alkyl, $-\text{COC}_{1-4}$ alkyl, COYC_{1-4} alkyl where Y is O, $\text{S(O)}_n\text{R}^{13}$ (where $n = 0, 1$ or 2) or NR^7 .

Provided that:

- One or more of the substituents on R³ must be aryl, heteroaryl or C₁₋₆alkyl (the latter group being substituted by aryl or heteroaryl);
 - When R³ is biphenyl X must be O or S;
 - When R³ is aryl substituted by C₁₋₆alkyl X must be O or S;
 - R³ cannot be 4-phenyl-1,3-thiazol-2-yl.
2. A compound according to claim 1 where X is S(O)_n where n is 0, 1 or 2.
 3. A compound according to claim 1 where X is S.
 4. A compound according to claims 1 to 3 where R¹ is halogen.
 5. A compound according to claims 1 to 3 where R¹ is NHCOR⁶.
 6. A compound according to claims 1 to 5 where R² is C₁₋₇alkyl.
 7. A compound according to claims 1 to 5 where R² is methyl.
 8. A compound according to claims 1 to 7 where R³ is phenyl optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, nitro, S(O)_nR⁴, OH, OR⁴, OS(O)_nR⁴, S(O)_nR⁴, SO₂NR⁵R⁶, CONR⁵R⁶, NR⁵R⁶, NR⁴SO₂R⁵, NR⁴CO₂R⁶, NR⁴COR⁶, NR⁴SO₂NR⁵R⁶, NHSO₂R⁵, NHCO₂R⁶, NHCOR⁶, NHCONR⁴, NHSO₂NR⁵R⁶, aryl, heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈cycloalkyl or C₁₋₆alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR⁸, NR⁵R⁶ or S(O)_nR⁷ where n = 0, 1 or 2.
 9. A compound according to claim 1 selected from:
 [3-(Biphenyl-4-ylsulfanyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid;
 [5-Fluoro-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]acetic acid;

[4-Acetylamino-3-(biphenyl-4-ylsulfanyl)-2-methyl-indol-1-yl]-acetic acid;
[4-Acetylamino-2-methyl-3-(4-oxazol-5-yl-phenylsulfanyl)-indol-1-yl]-acetic acid
and pharmaceutically acceptable salts thereof.

10. A compound of formula (I) according to any one of claims 1 to 9 for use in therapy.
11. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 9.
12. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 9.

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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-SE-151 85 Södertälje (SE).

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(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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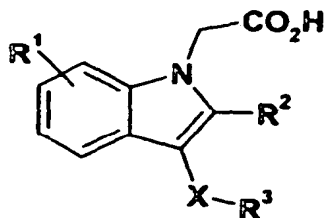
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(54) Title: BI-ARYL OR ARYL-HETEROARYL SUBSTITUTED INDOLES



(I)

(57) Abstract: The present invention relates to substituted indoles of Formula (I) useful as pharmaceutical compounds for treating respiratory disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/001951

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/30 A61K31/404 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/040114 A1 (OXAGEN LIMITED, UK) 6 May 2005 (2005-05-06) claim 12; tables 1,2; compounds 1-24 Compound 2 excluded by the proviso at the end of claim 1 -----	1-12
X	WO 03/101961 A (ASTRAZENECA AB [SE]; BONNERT ROGER [GB]; BROUGH STEPHEN [GB]; COOK TON) 11 December 2003 (2003-12-11) claims 1,5; compounds 1-59 page 48, paragraph 2 The compound claimed in claim 5 being excluded by the last proviso at the end of claim 1 -----	1-12
A	WO 2005/019171 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BONNERT ROGER VICTOR [GB]) 3 March 2005 (2005-03-03) the whole document -----	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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PCT/GB2007/001951

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/001951

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		US 2006264444 A1	23-11-2006